Cleavage Reactions of the Complex Ions Derived from Self-Complementary Deoxydinucleotides and Alkali-Metal Ions Using Positive Ion Electrospray Ionization with Tandem Mass Spectrometry

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The dissociation reactions of the adduct ions derived from the four self-complementary deoxydinucleotides, d(ApT), d(TpA), d(CpG), d(GpC), and alkali-metal ions were studied in detail by positive ion electrospray ionization multiple-stage mass spectrometry (ESI-MSⁿ). For the $[M + H]^+$ ions of the four deoxydinucleotides, elimination of 5'-terminus base or loss of both of 5'-terminus base and a deoxyribose were the major dissociation pathway. The ESI-MSⁿ spectra showed that Li^+ , Na^+ , and Cs^+ bind to deoxydinucleotides mainly by substituting the H^+ of phosphate group, and these alkali-metal ions preferred to bind to pyrimidine bases rather than purine bases. For a given deoxydinucleotide, the dissociation pathway of $[M + K]^+$ ions differed clearly from that of $[M + Li]^+$, $[M + Na]^+$, and $[M + Cs]^+$ ions. Some interesting and characteristic cleavage reactions were observed in the product-ion spectra of $[M + K]^+$ ions, including direct elimination of deoxyribose and HPO_3 from molecular ions. The fragmentation behavior of the $[M + K]^+$ and $[M + W]^+$ ($W = Li, Na, Cs$) adduct ions depend upon the sequence of bases, the interaction between alkali-metal ions and nucleobases, and the steric hindrance caused by bases. (J Am Soc Mass Spectrom 2004, 15, 689–696) © 2004 American Society for Mass Spectrometry

The interaction between organic compounds or biologically active molecules and alkali-metal cations in the gas phase has attracted much attention. Such interactions may relate to chemical and biological processes occurring in solution; for example, ion salvation, catalysis, transport through membranes, affinity of active compounds toward receptors, and antibiotic activity [1]. The alkali metal ions, especially Na^+ and K^+ , are of particular importance in the mechanism of action of some biomolecules. Alkali-metal ion affinities are a good basis for analysis and modeling of such interactions in complex systems. The affinities of alkali-metal ions with nucleobases have been investigated by both the kinetic method and threshold collision-induced dissociation mass spectrometry [2, 3]. On the basis of the research work on the formation of gas-phase ion-molecule complexes, Fujii [4] concluded

that the alkali-metal ion affinity generally followed the order of $Li^+ > Na^+ > K^+$.

Various mass spectrometric methods have been used to characterize metal ion biomolecular interaction at the molecular level, to determine the site of metal ion attachment to the biomolecular and its effect on altering the properties and reactivities of the biomolecule [1–17]. ESI-MS was shown to be an excellent means for characterizing of oligonucleotides [18, 19], and provide unambiguous identification of singly and multiply-charged ions of deprotonated, protonated, and metalated oligonucleotides.

Knowledge of the fundamental modes of metal ion binding to simple DNA and RNA compounds will greatly improve our understanding of how metal ions interact with nucleic acids of more complexity. Deoxydinucleotides are the smallest subunits in nucleic acids bearing sequence information of DNA.

The dissociation reactions of protonated molecular ions from 12 possible hetero- deoxyribonucleotides were previously studied using fast atom bombardment with tandem mass spectrometry [5, 6]. It was proposed

Published online February 27, 2004

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Scheme 1. Structures of self-complementary deoxydinucleotides.

that dissociation reactions of positive ions are influenced by a tertiary structure in which the phosphate oxygens, stabilized by interactions with the 3'-terminus base. Recently, we studied the fragmentation behavior of oligonucleotides by positive ion ESI-MS and ESI-MS/MS [20–22]. In order to investigate the difference of the interaction between alkali-metal ions and deoxydinucleotides with the same bases but different sequence, the cleavage reactions of the complex ions of self-complementary deoxydinucleotides, d(ApT), d(TpA), d(CpG) and d(GpC), with H^+ , Li^+ , Na^+ , K^+ , and Cs^+ were examined in detail by positive ion ESI-MSⁿ. The structures of these compounds are shown

in Scheme 1. The characterization and the difference of the cleavage reactions of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, and $[M + Cs]^+$ ions were obtained using collision-induced dissociation (CID) analysis with multiple-stage mass spectrometry.

Experimental

The deoxydinucleotide samples were synthesized using an Applied Biosystems 391s DNA Synthesizer, and were presented by Dr. Takayama from Yokohama City University. The samples were prepared and diluted to

Figure 1. Product-ion spectra of (a) $[M + H]^+$ at m/z 556, (b) $[M + Li]^+$ at m/z 562, (c) $[M + Na]^+$ at m/z 578, (d) $[M + K]^+$ at m/z 594, and (e) $[M + Cs]^+$ ions at m/z 688 derived from d(ApT).

Figure 2. Product-ion spectra of (a) $[M + H]^+$ at m/z 556, (b) $[M + Li]^+$ at m/z 562, (c) $[M + Na]^+$ at m/z 578, (d) $[M + K]^+$ at m/z 594, and (e) $[M + Cs]^+$ ions at m/z 688 derived from d(TpA).

Figure 3. Product-ion spectra of (a) $[M + H]^+$ at m/z 557, (b) $[M + Li]^+$ at m/z 563, (c) $[M + Na]^+$ at m/z 579, (d) $[M + K]^+$ at m/z 595, and (e) $[M + Cs]^+$ ions at m/z 689 derived from d(CpG).

10 pmol/ μ L in a solution of 1% CH₃COOH in 50/50 CH₃CN/H₂O. The solution with the same solvent was used as the mobile phase which was delivered at a flow rate of 5–10 μ L/min.

The experiments were performed on an ion-trap mass spectrometer (Finnigan LCQ, San Jose, CA), equipped with an ESI source and operated in the positive-ion mode as follows: spray voltage, 5.00 kV; capillary voltage, 7 V; heated capillary temperature, 200 °C; tube lens offset voltage, 30 V; sheath gas (N₂) flow rate: 35 arb (roughly 0.75 L/min). The CID spectra were obtained in the presence of a collision gas of He with the relative collision energies varying from 12 to 40%. (Nominal CID amplitude values in this instrument range from 0% to 100% relative collision energy corresponding to 0–5 V zero-to-peak resonant excitation potential).

Results and Discussion

In the ESI mass spectra of the four self-complementary deoxydinucleotides, besides $[M + H]^+$ ions (base peak), the metal ion adducts, $[M + Na]^+$ and $[M + K]^+$ can also be observed. The solutions of LiCl and CsI were mixed in the same volume with the 60 pmol/ μ L deoxydinucleotides in the solution of 1% CH₃COOH in 50/50 CH₃CN/H₂O, and when sprayed, this solution pro-

Figure 4. Product-ion spectra of (a) $[M + H]^+$ at m/z 557, (b) $[M + Li]^+$ at m/z 563, (c) $[M + Na]^+$ at m/z 579, (d) $[M + K]^+$ at m/z 595, and (e) $[M + Cs]^+$ ions at m/z 689 derived from d(GpC).

duced $[M + Li]^+$ and $[M + Cs]^+$ ions. $[M + Li]^+$ could be observed (base peak) for all of the four deoxydinucleotides, while only d(ApT) could produce $[M + Cs]^+$ with low abundance (4.0%) when both of Li⁺ and Cs⁺ ions are at the concentration of 10 pmol/ μ L. The concentration of Cs⁺ had to be increased by 6–60 times to produce $[M + Cs]^+$ ions for d(TpA), d(CpG), and d(GpC), but the relative abundances of $[M + Cs]^+$ derived from them were still very weak. A greater concentration of Cs⁺ was required to produce $[M + Cs]^+$ ions when the 3'-end of deoxydinucleotide was a purine base.

The product-ion spectra of $[M + H]^+$, $[M + K]^+$, and $[M + W]^+$ ($W = Li, Na, Cs$) ions derived from d(ApT), d(TpA), d(CpG), and d(GpC) are shown in Figures 1, 2, 3, and 4, respectively. $[M + K]^+$ and $[M + W]^+$ ions may come from coordinative, multisite binding between the metal cations and several cation-accepting groups such as hydroxyl and/or phosphate groups. For the $[M + H]^+$ ions of the four deoxydinucleotides, the major product ions result from loss of 5'-terminus base as neutral molecules (denoted as A, C, T, G) or elimination of both of the 5'-terminus base and a deoxyribose.

As shown in Figure 1a, the major product ions of $[M + H]^+$ derived from d(ApT) are $[M + H - A - \text{deoxyribose}]^+$ at m/z 323, $[M + H - \text{deoxyribose}]^+$ at

Scheme 2. The main difference in fragmentation of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, and $[M + Cs]^+$ proposed to account for the CID spectra of d(ApT).

m/z 458 and $[M + H - A]^+$ at m/z 421. The product-ion spectrum of m/z 323 (MS^3 mode) was measured to reconfirm the cleavage reaction of d(ApT), and the major product ions are $[M + H - A - \text{deoxyribose} - H_3PO_4 - H_2O]^+$ at m/z 207 and $[M + H - A - \text{deoxyribose} - T]^+$ at m/z 197.

For d(TpA), the product ions of the $[M + H]^+$ precursor consist of $[M + H - T - \text{deoxyribose}]^+$ at m/z 332, of the highest abundance, $[M + H - T]^+$ at m/z 430, $[M + H - A - \text{deoxyribose} - H_2O]^+$ at m/z 305 and $[M + H - A - \text{deoxyribose} - H_2O - HPO_3]^+$ at m/z 225 (see Figure 2a). In the product-ion spectrum of m/z 332 (MS^3 mode), the major product ion is $[A + H]^+$ at m/z 136.

Figure 3a shows the product ion spectrum of $[M + H]^+$ ion derived from d(CpG), in which $[M + H - C]^+$ at m/z 446 is observed to be the major product ion, and $[M + H - C - \text{deoxyribose}]^+$ at m/z 348 is also produced. In the product-ion spectrum of the ion of m/z 446 (MS^3 mode), the major product ions are $[M + H - C - \text{deoxyribose}]^+$ at m/z 348 and $[G + H]^+$ at m/z 152.

In the product-ion spectrum of $[M + H]^+$ ion of d(GpC), the major product ions are $[M + H - G]^+$ at m/z 406, which is the most abundant ion, and $[M + H - G - \text{deoxyribose}]^+$ at m/z 308. Differently from d(ApT), d(TpA), and d(CpG), d(GpC) can also lose 3'-terminus base to produce $[M + H - C]^+$ ion at m/z 446 with high abundance (see Figure 4a). In the product-ion spectrum of the precursor ion $[M + H - G]^+$ (MS^3 mode), the product ions $[M + H - G - \text{deoxyribose}]^+$ at m/z 308, $[M + H - G - H_2O]^+$ at m/z 388 can be observed.

The major product ions formed in the protonated dinucleotides systems are those resulted from loss of 5'-terminus base and a deoxyribose. The preferential elimination of the 5'-terminus base over similar bases at 3'-terminus, and the easier cleavage of the 3'-phosphate diester linkage over the 5'-linkage, suggest that the 3'-terminus base might be stabilized through hydrogen bonding interactions with phosphate group.

Based on the analysis of the product-ion spectra of $[M + W]^+$, we can find that, although the loss of the terminal bases remained as the major decomposition, the fragmentation behaviors of $[M + W]^+$ differed from that of the $[M + H]^+$ ions. The results suggest that the pyrimidine bases are stabilized when the deoxydinucleotides combined with Li^+ , Na^+ and Cs^+ .

Figure 1b, c, and e show the product-ion spectra of $[M + Li]^+$, $[M + Na]^+$, and $[M + Cs]^+$ derived from d(ApT). Similar to those of $[M + H]^+$, the major product ions are $[M + W - A]^+$ and $[M + W - A - \text{deoxyribose}]^+$, which resulted from loss of 5'-terminus adenine, and both the A and a deoxyribose. For $[M + H]^+$, $[M + H - A - \text{deoxyribose}]^+$ is the most abundant product ion, while $[M + Na - A]^+$ and $[M + Cs - A]^+$ are the most abundant in the product-ion spectra of $[M + Na]^+$ and $[M + Cs]^+$, indicating that the fragmentation varied regularly from $[M + Li]^+$ to $[M + Cs]^+$. The product-ion spectra of $[M + W - A - \text{deoxyribose}]^+$ ions show the different cleavage of $[M + W]^+$ ions from the $[M + H]^+$ ion. It was observed that the major product ions were $[M + W - A - \text{deoxyribose} - T]^+$ and $[M + W - A - \text{deoxyribose} - T - H_2O]^+$.

Scheme 3. The main differences in fragmentation of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, and $[M + Cs]^+$ proposed to account for the CID spectra of d(TpA).

For d(TpA), the presence of the most abundant ions $[M + W - A]^+$ and $[M + W - A - H_2O]^+$ indicates that the fragmentation of $[M + W]^+$ ions is characteristically dominated by the loss of 3'-terminus A or both of the A and a H_2O molecule (see Figure 2b, c, and e). It is noteworthy that the product ions resulting from loss of 5'-terminus thymine can not be observed. In the product-ion spectrum of $[M + Li]^+$ ion, the peak corresponding to $[M + Li - T - deoxyribose]^+$ at m/z 338 can be observed with the highest abundance. The major product ions of $[M + Li - T - deoxyribose]^+$ are $[M + Li - T - deoxyribose - A]^+$ and $[M + Li - T - deoxyribose - A - H_2O]^+$ (MS^3 mode). In the product-ion spectrum of $[M + Na - A - H_2O]^+$ ion (MS^3 mode), elimination of a deoxyribose to produce $[M + Na - A - H_2O - deoxyribose]^+$ ion at m/z 327 is a major cleavage reaction. The interesting results show that Li^+ , Na^+ , Cs^+ preferred to bind to thymine rather than adenine.

For d(CpG), the product-ion spectra of $[M + W]^+$ ions differ from $[M + H]^+$ ion as shown in Figure 3. In addition to $[M + W - C]^+$ and $[M + W - C - deoxyribose]^+$, ions resulting from loss of 3'-terminus G or both the G and H_2O are also formed, and the abundance of $[M + W - C]^+$ ion decreases clearly compared with that of $[M + H - C]^+$.

The major product ions of $[M + W]^+$ are very similar for d(GpC), in which the 5'-terminus G is the most favorable for expulsion, and the abundance of $[M + W - G - deoxyribose]^+$ ion increases. Unlike the $[M + H]^+$, eliminating cytosine become difficult, which can not be seen in the product-ion spectra of $[M + Li]^+$ and $[M + Na]^+$ (see Figure 4).

To investigate the difference of d(CpG) and d(GpC), we analyzed the product-ion spectra of $[M + W - G]^+$ ion (MS^3 mode) derived from both deoxydinucleotides. For d(CpG), the major product ions observed were $[M + Li - G - H_2O]^+$, $[M + Na - G - H_2O]^+$ and $[M + Cs - G - deoxyribose]^+$, respectively. However, a deoxyribose was eliminated from the $[M + W - G]^+$ ion derived from d(GpC) to produce $[M + W - G - deoxyribose]^+$.

Based on the analysis of the product-ion spectra of $[M + W]^+$ ions of the four self-complementary deoxydinucleotides, it appears that when deoxydinucleotides bind with Li^+ , Na^+ or Cs^+ ions, elimination of pyrimidine bases become difficult, while loss of purine bases is the dominating step for initial fragmentation, and often followed by elimination of a deoxyribose or H_2O . The facts mentioned above also indicate that Li^+ , Na^+ and Cs^+ attach to deoxydinucleotides mainly by substituting for the H^+ of phosphate group, and they prefer to binding with pyrimidine bases rather than purine bases. It can also be found that when 3'-terminus are pyrimidine bases, as in d(ApT) and d(GpC), the dissociation pathway of $[M + Li]^+$ is similar to that of $[M + Na]^+$. However, when purine bases are at the 3' terminus, as in d(TpA) and d(CpG), the fragmentation of $[M + Li]^+$ is not completely analogous with both of the fragmentation of $[M + H]^+$ and $[M + Na]^+$. It appears that the steric hindrance caused by the 3'-terminus purine bases prevent alkali-metal ions from substituting for the H in phosphate group, and a part of metal ions bind to the 5'-terminus bases.

Significant changes take place in the fragmentation behaviors of the $[M + K]^+$ complex ions, and the

Scheme 4. The main differences in fragmentation of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, and $[M + Cs]^+$ proposed to account for the CID spectra of d(CpG).

characterization of dissociation observed is different for the four deoxydinucleotides. The product-ion spectra of $[M + K]^+$, (Figure 1d–Figure 4d), show that the cleavage reactions are much more complex in the $[M + K]^+$ systems, including not only loss of 5'-terminus bases or a deoxyriboses but also elimination of water, deoxyribose, 3'-terminus base and metaphosphoric acid. The elimination of a deoxyribose or water is more favorable for the $[M + K]^+$ ions than for $[M + W]^+$.

Comparing the CID spectrum of $[M + K]^+$ ion of d(ApT) with that of d(TpA), we can see that their fragmentation patterns are quite different. For d(ApT), the abundance of the $[M + K - A]^+$ ion at m/z 459 is second highest, only weaker than that of $[M + K - H_2O]^+$ ion at m/z 576, and the $[M + K - T]^+$ ion can also be observed at fairly high abundance. In the product-ion spectrum of $[M + K - A]^+$ (MS^3 mode), the major product ion is $[M + K - A - \text{deoxyribose}]^+$ at m/z 361. The product-ion spectrum of $[M + K]^+$ derived from d(TpA) shows that it is more likely to fragment than d(ApT). The most abundant product ion at m/z 388 is formed by the loss of a neutral T and a HPO_3 molecule, and the abundance of $[M + K - T]^+$ decreases clearly. The major product ion of $[M + K - T - HPO_3]^+$ at m/z 388 is $[M + K - T - HPO_3 - H_2O]^+$ at m/z 370 (MS^3 mode). Elimination of an HPO_3 molecule is an interesting cleavage reaction, which can also be observed in the product-ion spectrum of $[M + K - A]^+$ ion at m/z 459 derived from d(ApT) to produce $[M + K - A -$

$HPO_3]^+$ at m/z 379 (MS^3 mode). Since the radius of K^+ ion is greater than that of Li^+ and Na^+ , it is more liable for K^+ to bind with bases and deoxyribose that are located on the exterior surface of the molecule. Schemes 2 and 3 illustrate the main difference in fragmentation of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$, and $[M + Cs]^+$ ions for d(ApT) and d(TpA), respectively.

The product-ion spectrum of $[M + K]^+$ ion of d(CpG) is more complicated than that of d(GpC). In addition to $[M + K - G]^+$, $[M + K - G - H_2O]^+$, $[M + K - C]^+$ and $[M + K - C - \text{deoxyribose}]^+$, the $[M + K - \text{deoxyribose}]^+$ ion is formed with the highest abundance. In the product-ion spectrum of $[M + K - \text{deoxyribose}]^+$ at m/z 497 (MS^3 mode), the major product ions are $[M + K - \text{deoxyribose} - H_2O]^+$ at m/z 479, $[M + K - \text{deoxyribose} - C]^+$ at m/z 386, $[M + K - \text{deoxyribose} - G]^+$ at m/z 346 and subsequent loss of H_2O . The fragmentation patterns of $[M + K]^+$ ion derived from d(GpC) are fairly simple. The main product ions at m/z 444 and 346 originate from successive loss of G and both of the G base and a deoxyribose, respectively. The $[M + K - \text{deoxyribose}]^+$ ion at m/z 497 originates from loss of deoxyribose directly. The major product ions of $[M + K - G]^+$ at m/z 444 (MS^3 mode) are $[M + K - G - H_2O]^+$ at m/z 426 and $[M + K - G - \text{deoxyribose}]^+$ at m/z 346 (base peak). These results indicate that when K^+ is attached to a deoxydinucleotide, the steric exclusion caused by G is greater than that caused by C. Thus, in the product-ion

spectrum of the $[M + K]^+$ ion derived directly from d(CpG), the $[M + K - \text{deoxyribose}]^+$ ion arises from a precursor ion in which K^+ binds to exterior bases of deoxydinucleotides molecules. However, the production spectrum of $[M + K]^+$ ion indicates that K^+ is easier to bind to the phosphate group in d(GpC) than in d(CpG), and the main fragmentation pathway is similar to that of $[M + Li]^+$, $[M + Na]^+$ and $[M + Cs]^+$ ions. The main differences in fragmentation of $[M + H]^+$, $[M + Li]^+$, $[M + Na]^+$, $[M + K]^+$ and $[M + Cs]^+$ ions derived from d(CpG) and d(GpC) proposed according to product ion analysis are shown in Schemes 4 and 5, respectively.

Based on the analysis of all the product-ion spectra, it appeared that when the 3'-terminus nucleobase is a pyrimidine base, as in d(ApT) and d(GpC), the steric exclusion that hinders K^+ from binding to the phosphate acid is fairly weak. Thus, the fragmentation of the $[M + K]^+$ ion is dominated by the neutral loss of the 5'-terminus nucleobase or both the 5'-terminus base and a deoxyribose. When the 3'-terminus nucleobase is a purine base, as in d(TpA) and d(CpG), the larger volume of purine base than that of the pyrimidine base and the correspondingly steric exclusion of purine base is greater than that of pyrimidine base. As the volume of Li^+ and Na^+ are smaller than that of K^+ , the steric exclusion caused by the 3'-terminus purine base did not preclude Li and Na^+ from binding to the phosphate, but did hinder K^+ from binding to the phosphate. K^+ attaches to deoxydinucleotides not only by binding to

the phosphate group, just as do Li^+ and Na^+ ions, but also by binding to several other sites (i.e., bases or deoxyribose). Thus, some peculiar cleavage reactions occur for both d(TpA) and d(CpG), which have 3'-terminus purine bases. The fragmentation behavior of the $[M + K]^+$ complex ions largely depend upon the sequence of bases, which provide the different binding site for the K^+ ion in the deoxydinucleotides.

It is noteworthy that the radius of Cs^+ is greater than that of K^+ , but the fragmentation behavior of $[M + Cs]^+$ ions of the four self-complementary deoxydinucleotides is quite different from that of $[M + K]^+$ but similar to $[M + Li]^+$ and $[M + Na]^+$. It appears that the volume of K^+ matches the vacancies between the two bases, so that K^+ mainly binds to the base groups, resulting in some characteristic fragmentation.

Conclusion

Results from this study showed that the fragmentation behavior of self-complementary deoxydinucleotides varied markedly due to the differences of the type and the sequence of bases. For $[M + H]^+$ ions of all the four deoxydinucleotides, elimination of 5'-terminus base or loss of both the 5'-terminus base and a deoxyribose are the major dissociation pathways. Li^+ , Na^+ and Cs^+ attach to deoxydinucleotides mainly by substituting for the H^+ of phosphate group, and they prefer to bind with pyrimidine bases rather than purine bases. The fragmentation pathway of $[M + Li]^+$ is similar to that of

$[M + Na]^+$ for the deoxydinucleotides with 3'-terminus pyrimide bases. However, for deoxydinucleotides with 3'-terminus purine bases, the fragmentation pathway of $[M + Li]^+$ was slightly different from that of $[M + H]^+$ and $[M + Na]^+$. In addition to the interaction between alkali-metal ions and nucleobases, 3'-terminus bases play a more important role in the fragmentation of $[M + W]^+$ ($W = Li, Na$ and Cs) ions than 5'-terminus bases. The fragmentation behavior of the $[M + K]^+$ complex ions largely depend upon the sequence of the bases, the interaction between K^+ and nucleobases and the steric hindrance caused by bases and K^+ itself. All of the facts mentioned above lead to different sites for K^+ ion binding in the deoxydinucleotides.

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